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Early goal-directed nutrition in ICU patients (EAT-ICU): protocol for a randomised trial

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ABSTRACT

INTRODUCTION: Extensive weight loss has been documented in intensive care unit (ICU) survivors, primarily as the result of muscle loss, leading to impaired physical function and reduced quality of life. The aim of the EAT-ICU trial is to test the effect of early goal-directed protein-energy nutrition based on measured requirements on short-term clinical outcomes and long-term physical quality of life in ICU patients.

METHODS: The EAT-ICU trial is a single-centre, randomised, parallel-group trial with concealed allocation and blinded outcome assessment. A total of 200 consecutive, acutely admitted, mechanically ventilated intensive care patients will be randomised 1:1 to early goal-directed nutrition versus standard of care to show a potential 15% relative risk reduction in the primary outcome measure (physical function) at six months (two-sided significance level $\alpha = 0.05$; power $\beta = 80\%$). Secondary outcomes include energy- and protein balances, metabolic control, new organ failure, use of life support, nosocomial infections, ICU- and hospital length of stay, mortality and cost analyses.

CONCLUSION: The optimal nutrition strategy for ICU patients remains unsettled. The EAT-ICU trial will provide important data on the effects of early goal-directed protein-energy nutrition based on measured requirements in these patients.

FUNDING: The EAT-ICU trial is funded by Copenhagen University Hospital, Rigshospitalet and Fresenius Kabi A/S and supported by The European Society for Clinical Nutrition and Metabolism (ESPEN).

TRIAL REGISTRATION: Clinicaltrials.gov identifier no. NCT01372176.

Advances in the treatment of intensive care patients have resulted in a reduction in overall mortality after critical illness. A significant part of these surviving patients experience impaired physical function, which reduces their quality of life in the years after discharge [1-3]. Studies have documented average weight losses of 20% in survivors of long-term admission at the intensive care unit (ICU), primarily as a result of extensive muscle loss [3-5]. Patients indicate loss of muscle mass as the primary cause of impaired function and reduced quality of life [1, 3, 6]. The synergetic effect of immobil-

isation, medicines and inflammatory stress on muscle atrophy may be further enhanced by insufficient provision of nutrients during intensive care. Still, the role of nutrition is less investigated.

Recent randomised trials have focused mainly on route of nutrition support, timing and whether to provide patients with a hypo- or eucaloric nutritional therapy [7-10]. Results are diverging, probably as a result of different feeding protocols, difference in case-mix and mortality rates. Common to all the trials, though, was less attention to the provision of protein.

Presently, it remains unclear whether supplementary parenteral nutrition (PN) should be used for ICU patients when nutritional targets are not met with enteral nutrition (EN). Supplementing EN with PN based on indirect calorimetry in the early course of ICU admission improved clinical outcome (survival and infections) in two randomised trials [7, 9]. In contrast, another large study found increased rates of complications with early supplementary PN in ICU patients [8], however, in this trial indirect calorimetry was not employed. In none of the trials nitrogen balances were measured, and protein/amino acids were provided in doses below those suggested in recent observational studies [11, 12]. Adequate amounts of protein might accelerate recovery. Based on current research, randomised trial focussing on providing adequate amounts of protein in conjunction with combined EN and PN based on indirect calorimetry early in the admission is needed to fill the knowledge gap [13].

Therefore, in the present study, patients will be randomised to either standard nutritional therapy or early goal-directed nutrition. The early goal-directed nutrition therapy focuses on both energy and protein, including measured requirements (indirect calorimetry and nitrogen balance) and early initiation of supplementary PN to meet 100% of requirements from day 1 after randomisation.

Aim

The aim of the EAT-ICU trial is to investigate the effect of early goal-directed nutrition versus standard nutritional therapy during intensive care on short-term clinical outcome and long-term quality of life, including physical function.

PROTOCOL ARTICLE

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ABBREVIATIONS

6S = Scandinavian Starch for Severe Sepsis/Septic Shock Trial
 CRRT = continuous renal replacement therapy
 EN = enteral nutrition
 ESPEN = The European Society for Clinical Nutrition and Metabolism
 GCP = good clinical practice
 ICU = intensive care unit
 PCS score = physical component summary score
 PN = parenteral nutrition
 SAR = serious adverse reaction
 SF-36 = short form quality of life questionnaire
 SNOSE = sequentially numbered, opaque, sealed envelopes
 SOFA score = sepsis-related organ failure assessment score
 SUSAR = serious unexpected adverse reactions



TABLE 1

Inclusion- and exclusion criteria for the Early Goal-Directed Nutrition in ICU Patients Trial.

Inclusion criteria

Patients are randomised, included and dosed no later than 24 h after admission to the ICU
 The following criteria must be met to be eligible for inclusion:
 Age \geq 18 yrs
 Acutely admitted to the ICU
 Expected length of stay in ICU > 3 days
 Mechanically ventilated, which enables indirect calorimetry
 Have a central venous catheter wherein parenteral nutrition can be administered
 Proxy consent obtained
 The ability to read and understand Danish

Exclusion criteria

Contraindications to use enteral nutrition as judged by the clinicians
 Contraindications to use parenteral nutrition, e.g. hypersensitivity towards fish-, egg- or peanut protein, or any of the active substances in the PN products
 Receiving a special diet
 Burn injury of more than 10% of the total body surface area
 Severe hepatic failure (Child-Pugh class C) or severe hepatic dysfunction: bilirubin concentration \geq 50 μ mol/l (3 mg/dl) + alanine aminotransferase concentration \geq 3 \times upper reference value
 Traumatic brain injury
 Diabetic ketoacidosis
 Hyperosmolar non-ketotic acidosis
 Known or suspected hyperlipidaemia
 BMI \leq 17 kg/m² or severe malnutrition
 Pregnancy
 The clinician finds that the patient is too deranged (circulation, respiration, electrolytes etc.) or that death is imminent

BMI = body mass index; ICU = intensive care unit.

Hypothesis

Early goal-directed protein-energy nutrition provided on the basis of measured requirements will improve short-term clinical outcome as well as long-term quality of life.

METHODS

This single-centre trial is conducted at the Department

of Intensive Care, Rigshospitalet, Denmark, using a computer-generated allocation sequence, concealed allocation and blinded outcome assessment of patients. Patients are randomised 1:1 to control or intervention groups, stratified for the presence of haematological malignancy as mortality is markedly higher in this group than in other intensive care patients (70% at 90 days in the 6S trial [14]). Patients will be screened and included according to the criteria presented in **Table 1**. Please see **Figure 1** for a flow diagram of the trial.

Randomisation

Two computer-generated lists for randomisation, with variable block size, have been prepared by a person who does not otherwise participate in the trial. Investigators draw sequentially numbered, opaque, sealed envelopes (in accordance with the SNOSE principles [15]) from one of two boxes in a consecutive order depending on the presence or absence of haematological malignancy.

Blinding

The allocated nutrition strategy is not masked for research- and clinical staff caring for the patient. Investigators assessing rates of nosocomial infections and quality of life at six months are masked to the intervention.

Primary outcome measure

- Physical function six months after randomisation assessed as physical component summary (PCS) score of the short form (SF)-36 v. 1.0 obtained by phone-interview by a person blinded to the intervention. For details on the SF-36 questionnaire, please go to www.sf-36.org.

Secondary outcome measures

Clarification: Life support outcomes will be analysed as percent of days alive without the use of life support in the 90-day period, in order to reduce the risk of survival bias.

- Accumulated energy- and protein balance
- New organ failure in the ICU (Y/N) (defined as a sepsis-related organ failure assessment (SOFA) score of 3 or above in any of the categories [16], excluding Glasgow Coma Scale Score) in patients who did not have the particular organ failure at randomisation
- Metabolic control: Accumulated insulin administration to maintain blood glucose \leq 10 mmol/l and rates of severe hyper- and hypoglycaemia (blood glucose > 15 mmol/l and \leq 2.2 mmol/l, respectively)
- Rate of nosocomial infections (Y/N, yes if positive in one of six specific types of infections) [17]
- New onset of renal replacement therapy (Y/N)
- Percent of days alive without renal replacement therapy at day 90

- Percent of days alive without mechanical ventilation at day 90
- Percent of days alive without inotropic/vasopressor support at day 90
- Length of stay in ICU and hospital among survivors at six months
- 28-day, 90-day and six-month mortality, and survival status for all patients six months after randomisation of the last patient
- Mental component summary score of SF-36
- Serious adverse reactions (SARs) in the ICU (allergic reactions and elevated plasma levels of liver enzymes)
- Cost analyses according to [18, 19].

Trial interventions

Intervention group

Primary targets:

- Goal: Delivering 100% of patient-specific requirements throughout the entire ICU stay

- Initiation of nutrition ≤ 24 hours of admission (EN + PN)
- Measured energy and protein requirements (indirect calorimetry, 24-hour urinary urea).

EN is gradually increased over the first days of admission. Supplementary PN is given to reach full requirements.

Energy requirement

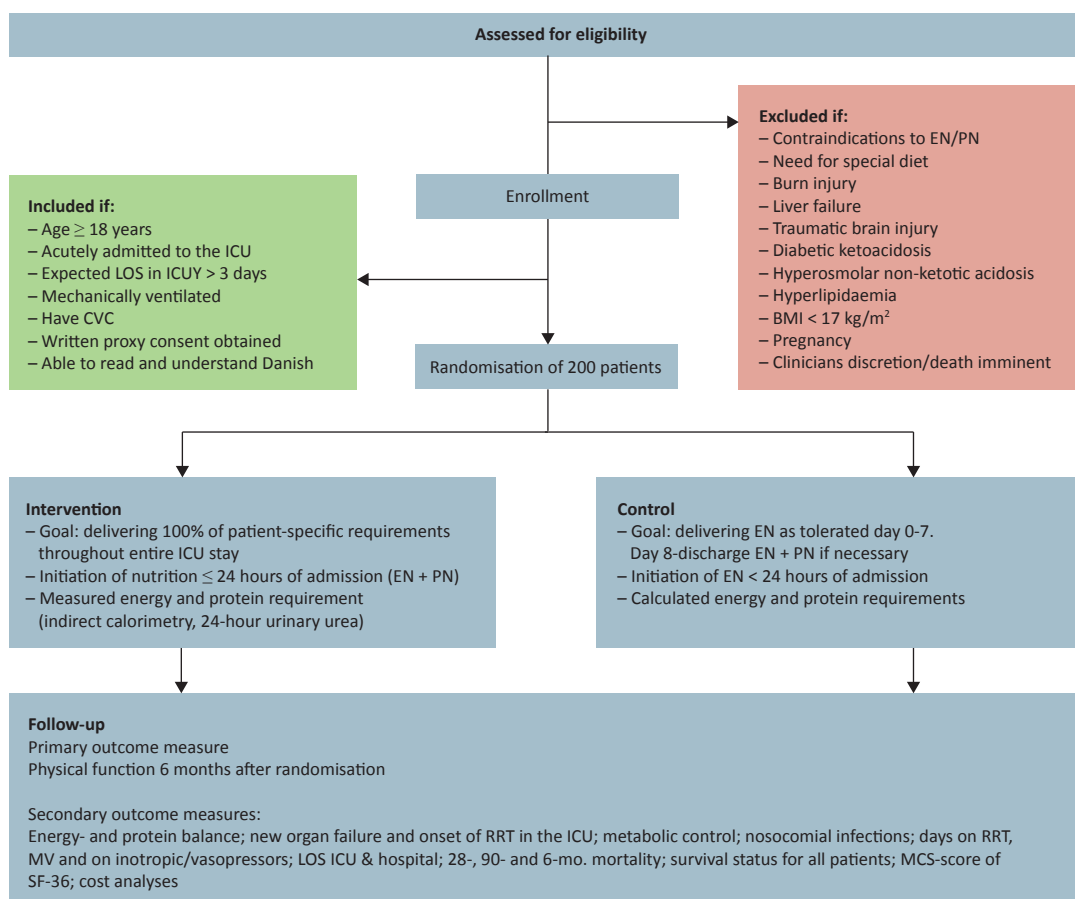
Measured using indirect calorimetry (Quark RMR Indirect Calorimeter from COSMED) as soon as possible after inclusion and hereafter every other day.

Protein requirement

Determined from the preceding day's 24-hour urinary urea using Bistran's Equation. A min. of 1.5 g protein/kg/day is provided, also when 24-hour urinary urea is not available/applicable (continuous renal replacement



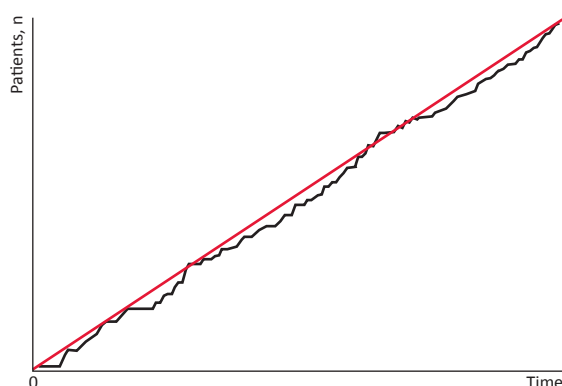
FIGURE 1



Flow diagram for the Early Goal-Directed Nutrition in ICU Patients Trial.

FIGURE 2

Inclusion in the Early Goal-Directed Nutrition in ICU Patients Trial by 4 April 2016; 203 of 203 patients included.



therapy (CRRT) or intermittent haemodialysis). Protein provision will be reduced below 1.5 g/kg/day at p-urea > 20 mmol/l.

Control group

Primary targets

- Goal: Delivering EN as tolerated by patient until day 7. Supplementary PN may be given by day 8
- Initiation of early EN (≤ 24 hours of admission)
- Calculated energy and protein requirements (25 kcal and 1.2 g protein per kg per day as stated in the guidelines from The European Society for Clinical Nutrition and Metabolism (ESPEN).

EN is gradually increased over the first days of admission as tolerated to reach the calculated energy goal. If EN fails to reach energy goals by day 7, supplementary PN may be initiated at day 8 to reach calculated requirements.

Monitoring of included patients

Glycaemic control is carried out in accordance with best evidence, targeting a blood glucose of 6–10 mmol/l. Gastric residual is monitored every 4–6 hours. Flow rate of EN will be reduced, and prokinetic therapy may be initiated at the clinicians' discretion at residuals between 150 and 500 ml.

P-triglycerides are measured on admission and hereafter on Mondays, Wednesdays and Fridays. Sodium and potassium are monitored daily; phosphate, magnesium and zinc twice a week, and substituted as needed. Trace elements and vitamins are given daily to all patients receiving PN.

Concomitant treatment

All other interventions and medical treatments are at the discretion of the treating clinicians.

Patient withdrawal

Patients may be withdrawn from the trial at any time if consent is retracted by the person giving proxy consent, next of kin or by the patient. The person withdrawing consent will be asked for permission to use the data acquired prior to withdrawal and to obtain data for the primary outcome measure and mortality. If this is achieved, the patient will be included in the final analyses. If the person declines, all data will be destroyed, and a new patient will be randomised to attain the full sample size. Patients who are withdrawn from the intervention protocol will be followed up for the primary endpoint and analysed as the remaining patients. Intention-to-treat and per-protocol analyses will be performed.

Suspension of nutrition strategy

The nutrition strategy according to randomisation can be suspended at any given time by the treating clinician or if one or more of the following potential complications occur:

- Severe hepatic dysfunction
- SAR or suspected unexpected serious adverse reaction (SUSAR)
- The clinical status of the patient requires unique nutritional treatment.

Severe adverse reactions

SARs are recorded as:

- Allergic reactions
- Elevated plasma levels of liver enzymes
- SUSARs: serious adverse events not described in the summaries of product characteristics for the nutrition products.

Statistics

A total of 200 patients will be included to show a 15% relative risk reduction in the primary endpoint (physical function) after six months (significance level $\alpha = 0.05$; power $\beta = 80\%$). The power calculation is based on data for physical function (PCS score) and six-month mortality extracted from our own published data [1] and the clinical database of the Department of Intensive Care (CIS v. 3.7.1, Daintel, Copenhagen). Control event rates were set to a PCS score of 37.5, standard deviation: ± 10.65 and a six-month mortality of 40%. The detailed statistical analysis plan is published online and is publically available [20].

Data handling and record keeping

Data are handled according to the rules and regulations of the Danish Data Protection Agency. All data are registered from source data and entered into a database by

trained personnel and will be retained at the trial site for 15 years. Details on data registered in the trial are published online and are publically available [20].

Monitoring

The trial is externally monitored by the good clinical practice (GCP) Unit, University of Copenhagen, according to EU Directive 2001/20, and adheres to the statutory order of GCP. Details on the plan for monitoring of the trial are published online and are publically available [20].

Ethical considerations

The trial adheres to the latest version of the Helsinki Declaration from 2010. The trial protocol was approved by the Danish Ethics Committee (Case no. 1300461), the Danish Medicines Agency (Eudract no. 2011-002547-94) and the Danish Data Protection Agency before inclusion of the first patient. It is the opinion of the steering committee that the benefits for the individual patient by participating in the trial will outweigh the potential risks.

Informed consent

Patients are enrolled after informed consent. As patients are unconscious at admission, and the trial requires immediate initiation, inclusion is done after proxy consent (two physicians, who are independent of the trial). As soon as possible, next of kin and the general practitioner of the patient/the Danish Health Authority are asked for consent. Eventually, informed consent from the patient is obtained when/if the patient regains consciousness.

Duration

The last patient was included on 4 April 2016, one week after the submission of this manuscript (Figure 2). We expect completion of six-month follow-up of the last randomised patient in October 2016.

Timeline

- 2012-2013: Applications for funding. Submission to Ethics Committee, Danish Medicines Agency and the Danish Data Protection Agency. Development of CRFs and data management tools and plan for monitoring
- 2013-2016: Inclusion of patients
- 2016-2017: Data analyses, writing of manuscript and publications.

Publication plan

Upon completion of the trial the results will be submitted to one of the major international peer-viewed journals regardless of the nature of the results.

Finances

The EAT-ICU trial is funded by Copenhagen University Hospital, Rigshospitalet and Fresenius Kabi A/S and sup-

ported by The European Society for Clinical Nutrition and Metabolism (ESPEN). None of the funding sources will have any influence on trial design, trial execution, data handling, analyses or publication.

Trial registration: Clinicaltrials.gov identifier no. NCT01372176.

DISCUSSION

Optimal nutrition for the ICU patient remains unsettled. In the EAT-ICU trial we test a strategy of an optimised protein-energy nutrition based on measured requirements with the aim of improving short-term clinical outcome as well as long-term physical function.

The strength of the study is the multimodal nutrition therapy testing the conjunction of adequate provision of both energy and protein given based on measured requirements. Such a nutritional therapy has not been tested in any of the previous randomised trials published in the recent years. The obvious limitations of the trial are the single-centre design, the relatively limited sample size and the fact that clinicians, patients and investigators are not blinded to the intervention. Thus, the results of the EAT-ICU should be interpreted with some caution.

Trial status

The trial was initiated on 24 June 2013 and inclusion of patients was concluded on 4 April 2016. A total of 586 patients have been screened and 203 patients are included in total (Figure 2).

Competing interests

None.

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